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IRIS Assessment Plan of Nitrate and Nitrite

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1. INTRODUCTION

The IRIS Program is undertaking a reassessment of the health effects of nitrate and nitrite. Nitrate and nitrite were included on the December 2015 IRIS Program multi-year agenda as chemicals with high priority for assessment development (https://www.epa.gov/iris/iris-agenda), largely because of interest in an updated health assessment by the Office of Water.

As noted in the multi-year agenda, prior to the initiation of an assessment, the IRIS Program consults with EPA program and regional offices to define the scope of the assessment, including the nature of the hazard characterization needed, identification of the most important exposure pathways, and level of detail needed to inform program and regional office decisions. Based on the scope defined by EPA, the IRIS Program undertakes problem formulation activities in order to frame the scientific questions that will be the focus of the assessment, which is conducted using systematic review methodology.

This document presents a draft assessment plan for nitrate and nitrite, including a summary of the IRIS Program's scoping and initial problem formulation conclusions, objectives and specific aims of the assessment, draft PECO (Population, Exposure, Comparators, and Outcomes) statement, and identification of key areas of scientific complexity. Brief background information on uses and potential for human exposure is provided for context. This document also discusses how EPA will consider recent authoritative reviews, in particular the Agency for Toxic Substances and Disease Registry's draft *Toxicological Profile for Nitrate and Nitrite* (ATSDR, 2015) and the International Agency for Research on Cancer monograph on nitrate and nitrate (IARC, 2010).

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Nitrate (NO_3^-) and nitrite (NO_2^-), naturally occurring anions in the environment, play an essential role in the Earth's nitrogen cycle. Since 1950, human sources of nitrogen have increased substantially, creating a surplus of nitrate/nitrite globally that has superseded natural sources by about 30% (Fields, 2004). Nitrate salts are mainly used as nitrogen fertilizers, and in industrial explosives, fireworks, and glass making, whereas nitrites are largely used as preservatives for meat and fish curing and as color fixatives (IARC, 2010; Pokorny L, 2006).

Nitrates account for the majority of available total nitrogen in both ground and surface waters; nitrite levels are generally low in both (DeSimone, 2009). The background level of nitrate in groundwater is typically below 10 mg/L (IARC, 2010). Due to human activities, however, environmental concentrations of nitrate and nitrite are higher (ATSDR, 2015). According to monitoring data obtained during EPA's second Six-Year Review of National Primary Drinking Water Regulations, nitrate was detected in approximately 70% of drinking water systems at a median concentration of approximately 2–3 mg nitrate-nitrogen/L; maximum concentrations in ground and surface waters were 99 and 48.5 mg nitrate-nitrogen/L, respectively. Nitrite was detected in approximately 22% of drinking water systems at a median concentration of 0.02 mg nitrite-nitrogen/L (U.S. EPA, 2009). Populations served by private well water, especially shallow wells in agricultural areas, may be exposed to nitrate at levels several times higher than those served by public water systems (DeSimone, 2009; Ward, 2009). Drinking water is generally a minor source of exposure to nitrite (IARC, 2010).

The main source of exposure to ingested nitrate is vegetables, with leafy vegetables making up nearly 80% of nitrate exposure in an average person's diet. Other sources of ingested nitrate include cured meats/fish, cereal grains, dairy products, and beer (ATSDR, 2015; IARC, 2010). Endogenous sources account for approximately 80% of all nitrites in the human body, as 5–8% of the total nitrate intake is converted into nitrite (WHO, 2016; Mensinga et al., 2003).

2.2. SCOPING SUMMARY

The IRIS Program previously conducted evaluations of the oral health effects of nitrate and nitrite; oral reference doses (RfDs) for nitrate[1] and nitrite[2] were posted to the IRIS database in 1991 and 1987. These RfDs were based on surveys of clinical cases of methemoglobinemia in infants

[1] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0076_summary.pdf
[2] https://cfpub.epa.gov/ncea/iris/iris_documents/doc2uments/subst/0078_summary.pdf

associated with ingestion of nitrate-containing drinking water conducted in the early 1950s (Walton, 1951; Bosch et al., 1950). Since 1987, a growing body of literature indicates potential associations between nitrate/nitrite exposure and other noncancer health effects. Some epidemiological studies also suggest an increased risk of cancer, especially gastric cancer, associated with dietary nitrite exposure (ATSDR, 2015). Cancer risk associated with nitrate or nitrite exposure is complicated by the fact that, under conditions of concurrent exposure to amines or amides or low levels of antioxidants, endogenous nitrosation could occur, leading to the formation of carcinogenic nitroso compounds (ATSDR, 2015; IARC, 2010). IARC concluded that ingested nitrate or nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans (Group 2A) (IARC, 2010).

During scoping, the IRIS Program met with EPA program and regional offices that had interest in an updated IRIS assessment for nitrates and nitrites to discuss specific assessment needs for an updated assessment. A summary of input from this outreach is provided in Table 1.

Table 1. EPA program or regional office interest in nitrate/nitrite assessment

EPA program or regional office[1]	Oral	Inhalation	Anticipated uses/interest
Office of Water	✓		Six-year review of the National Primary Drinking Water (NPDW) regulations
Region 5[1]	✓		Evaluation of special provision of the NPDW regulation [40 CFR 141.11(d)] allowing, at the discretion of the state, non-community water systems to exceed the nitrate MCL

[1]Region 5 serves Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin, and 35 Tribes.

The Office of Water regulates nitrates and nitrites under the National Primary Drinking Water Regulations (40 CFR 141, 142); the current maximum contaminant levels (MCLs) for nitrate and nitrite, promulgated in 1991, are 10 mg/L and 1 mg/L (as nitrogen), respectively (40 CFR 141.62; 56 FR 3594, January 30, 1991). An updated health assessment of nitrate and nitrite will be considered in the next Six-Year Review cycle for National Primary Drinking Water Regulations. A provision of the current regulation [40 CFR 141.11(d)] allows, at the discretion of the state, non-community water systems to exceed the nitrate MCL up to 20 mg/L if the supplier can demonstrate that the water will not be available to children under 6 months of age and that no adverse health effects will result. The availability of more recent health effects literature published since 1991 raises questions about whether the current MCLs for nitrate and nitrite and the provision allowing exceedance of the nitrate MCL up to 20 mg/L provide adequate health protection.

Based on input received during scoping, the IRIS assessment will include evaluation of both cancer and noncancer human health hazards associated with ingested nitrate and nitrite. Because the association between nitrate/nitrite and methemoglobinemia has been well established (Ward et al., 2005; Walton, 1951) a systematic review to examine this association will not be conducted. For this effect only, the assessment will focus only on the quantitative relationship between nitrate/nitrite exposure and methemoglobinemia. For cancer, EPA will develop a qualitative assessment of the carcinogenic potential of nitrate and nitrite, and will explore the feasibility of developing a quantitative assessment. EPA anticipates that the quantitative cancer assessment will be particularly challenging given the influence of concurrent exposure to dietary sources of nitrosatable compounds and antioxidants, and the number of epidemiology studies that investigated associations between nitrate or nitrite exposure and cancer at different sites (see Table 3)

Assessment of the health effects of nitrate and nitrite following inhalation and dermal routes of exposure will not be included in the scope of this assessment. Inhalation and dermal exposures to nitrate or nitrite in the general population are expected to be negligible compared to oral exposure. Focusing on the health effects associated with oral exposure to nitrate and nitrite is also consistent with the needs of EPA programs and regional offices.

This assessment will address inorganic forms of nitrate and nitrite, and will specifically consider health effects information for the compounds included in Table 2. These compounds are the most common nitrate and nitrite salts in the environment (ATSDR, 2015). These five nitrate/nitrite compounds were also the subject of two recent health assessments of nitrate and nitrite (ATSDR, 2015; IARC, 2010). The decision to develop the assessment of nitrate/nitrite using health effects information for these five compounds was also based on known general population exposure to these five compounds and availability of epidemiology or toxicology information. Specifically, ammonium nitrate is a leading nitrogen fertilizer, and for this reason it has been used in toxicological studies as a component of "California mixture" and "Iowa mixture," two mixtures representative of groundwater contamination by fertilizers and pesticides and used for simulations of environmental exposures to pesticides mixtures. Potassium nitrate, potassium nitrite, sodium nitrate, and sodium nitrite are all used as food additives to cure meats. Sodium nitrate and sodium nitrite have been used in animal toxicology and carcinogenicity studies performed by the National Toxicology Program (NTP).

Table 2. Nitrate/nitrite compounds considered in this assessment

Compound	Chemical formula	CAS Number
Ammonium nitrate	NH_4NO_3	6484-52-2
Sodium nitrate	$NaNO_3$	7631-99-4
Sodium nitrite	$NaNO_2$	7632-00-0
Potassium nitrate	KNO_3	7757-79-1
Potassium nitrite	KNO_2	7758-09-0

2.3. PROBLEM FORMULATION

A preliminary literature survey was performed using health assessments produced by other federal, state, and international health agencies (WHO, 2016; ATSDR, 2015; Health Canada, 2013; IARC, 2010; IPCS, 2005; Cal/EPA, 2000) to identify noncancer and cancer health outcomes whose possible association with exposure to nitrate/nitrite has been investigated.

In particular, the ATSDR (2015) draft *Toxicological Profile for Nitrate and Nitrite*, as the most recent authoritative health agency assessment, was relied on to identify the pertinent health effects literature through 2015. Because ATSDR (2015) updated the comprehensive review of the cancer epidemiology literature provided in IARC (2010) (i.e., literature published up to approximately 2007), the IARC monograph was also used to identify the cancer literature. The numbers of animal and human studies cited in ATSDR (2015) and IARC (2010) by health effect category were tallied as a measure of the extent to which the association between a given health effect and nitrate/nitrite exposure has been investigated (see Table 3).

Table 3. Summary of the number of studies cited in ATSDR (2015)[a]

Outcomes	Human Studies				Animal Studies					
	Occupational epidemiology studies	General population epidemiology studies	Controlled exposure studies	Case reports and case series reports	Chronic	Subchronic	Short-term	Acute	Multi-generational	Gestational
Cancer		>60[b]			13					
Cardiovascular		1	1	3						
Dermal and ocular				1						
Developmental		14							2	6
Endocrine (thyroid)		6	1		4	3	1			
Gastrointestinal	1			7	5	1				
Hematological		>25	3	>10	4	6	3	1		
Hepatic					3			2		
Immunological										
Metabolic disease (type 1 diabetes)		8								
Musculoskeletal										
Neurological and sensory			1	6	1	1			1	
Renal					1					
Reproductive			3		2	2			1	
Respiratory										
Other systemic toxicity[c]					9	2	1		1	

[a] The numbers represent the numbers of studies that investigated a particular health effect, and not the number of studies that identified a positive association with exposure to nitrate or nitrite. If a journal article or

report included, for example, a study in both rats and mice, it was counted as 2 studies.
[b] More than 50 epidemiologic studies that examined the association between nitrate/nitrite intake and cancer were cited in the 2010 IARC Monograph (IARC, 2010); an additional 13 selected cohort and case-control studies were identified in the ATSDR (2015) Toxicological Profile that were published after the literature search conducted by IARC.
[c] Body weight

2.4. HEALTH OUTCOMES TO BE EVALUATED

Based on the preliminary literature survey (i.e., the secondary sources that were used to develop Table 3), EPA anticipates that a systematic review will be conducted for the following health effect categories:

- Hematological effects
- Thyroid effects (endocrine effect)
- Type 1 diabetes (metabolic effect)
- Developmental effects
- Reproductive effects
- Cancer

For these health effect categories, the available epidemiology and/or experimental animal studies include multiple studies or in multiple species, and are likely to be sufficient for drawing conclusions about human hazard. Positive findings reported for other health effects categories (e.g., gastrointestinal, hepatic, and nervous system) were generally limited to a few studies, some with study design deficiencies, and were generally inconsistent. Therefore, EPA anticipates that a systematic review for health effect categories other than the six identified above will not be undertaken unless additional evidence of a positive association is identified upon review of references identified during the comprehensive literature search.

Literature screening revealed a number of studies reporting potential association between nitrate/nitrite exposure and beneficial cardiovascular outcomes. Because IRIS assessments focus on the adverse effects associated with exposure to environmental chemicals, a systematic review of the potential beneficial outcomes to the cardiovascular system associated with the intake of nitrate or nitrite will not be included in this assessment.

3. OVERALL OBJECTIVES, SPECIFIC AIMS AND DRAFT PECO STATEMENT

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for nitrate and nitrite to support development of toxicity values. This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature for these chemicals and consideration of relevant mechanistic evidence. The evaluations will be based on EPA guidance.[3] The systematic review protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims and PECO statement.

3.1. SPECIFIC AIMS

- Identify epidemiological and experimental animal literature pertaining to the health hazards of nitrate and nitrite as outlined in the PECO statement. ATSDR's draft *Toxicological Profile of Nitrate and Nitrite* (ATSDR, 2015) and the International Agency for Research on Cancer monograph on nitrate and nitrate (IARC, 2010) will serve as starting points to identify PECO-relevant evidence published through 2015. A literature search update will be performed to identify new health effects references for nitrate/nitrite published since the literature searches conducted by ATSDR and IARC.
- An iterative approach will be used to determine which mechanistic studies are most important to also summarize, based on factors such as robustness of the evidence in humans and animals, likelihood to impact evidence synthesis conclusions for human health, and directness or relevance of the model systems.
- Conduct study evaluation (risk of bias and sensitivity) for individual epidemiological and animal studies.
- Extract data on relevant health outcomes from epidemiological and experimental animal studies included based on the study evaluation. Mechanism or mode of action evidence will be briefly summarized when possible by relying on other published authoritative sources, e.g., public health agency reports and expert review articles.
- Synthesize the evidence across studies, assessing similar health outcomes using a narrative approach or meta-analysis (if appropriate). Where possible, EPA will also explore ways to take advantage of ATSDR and IARC synthesis of health effects evidence.

[3] EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/

- For each health outcome, express confidence in conclusions from across studies (or sub-sets of studies) within human and animal evidence streams according to one of the following statements: Robust, Moderate, Slight, Indeterminate, or Compelling evidence of no effect. Each evidence stream will be evaluated separately.
- For each health outcome, integrate results across evidence streams to conclude whether a substance is hazardous to humans. Identify and discuss issues concerning potentially sensitive populations.
- Derive toxicity values as supported by the available data. For nitrate and nitrite anions separately, consideration will be given to deriving RfDs and, if feasible, a cancer slope factor, using statistical approaches that support quantitative risk assessment.
- Characterize uncertainties and identify key data gaps and research needs, e.g., related to limitations of the evidence base, limitations of the systematic review, consideration of dose-relevance and pharmacokinetic differences when extrapolating findings from animal studies to human exposure levels.

3.2. DRAFT PECO STATEMENT

A PECO (Population, Exposure, Comparators, and Outcomes) statement (Table 4) is used as an aid to focus the research question(s), search terms, and inclusion/exclusion criteria in a systematic review. The draft PECO statement for nitrate and nitrite was based on (1) review of information accompanying the nomination of the chemical for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will meet Agency needs, (3) preliminary review of the health effects literature for nitrate and nitrite (primarily reviews and authoritative health assessment documents) to identify the major health hazards associated with exposure to nitrate and nitrite and key areas of scientific complexity.

Table 4. PECO (Populations, Exposures, Comparators, Outcomes) statement

PECO element	Evidence
Population	**Human:** Any population (children, general population, occupational, high exposure from an environmental source). As children younger than 6 months appear to be a sensitive population, this population will be emphasized during review. The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, or ecological. Note: Case reports and case series will be tracked during study screening but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if there are no or few more informative study designs available. Case reports can also be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
	Animal: Non-human mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal and adult stages).
	Non-mammalian model systems/in vitro/in silico: Non-mammalian model systems (e.g., fish, amphibians, birds, *C. elegans*, etc.): Human or animal cells, tissues, or biochemical

	reactions (e.g., ligand binding assays) with in vitro exposure regimens; bioinformatics pathways of disease analysis; or high throughput screening data. An iterative approach is used to prioritize inclusion of these studies for full-text retrieval and evidence synthesis based on likelihood to impact evidence synthesis conclusions for human health.*
Exposure	Exposure to specific nitrate/nitrite compounds including (CASRN): ammonium nitrate (6484-52-5), potassium nitrate (7757-79-1), potassium nitrite (7758-09-0), sodium nitrate (7631-99-4), sodium nitrite (7632-00-0), inorganic nitrate/nitrite in drinking water and inorganic nitrate/nitrite in foods. **Human and animal**: Exposure routes to be considered are any oral exposures. Where possible, exposures will be assessed separately for drinking water and dietary nitrate/nitrite. Other exposure routes, including inhalation, dermal, or injection, will be tracked during title and abstract as “supporting information.”
	In vitro: Exposure via growth or assay medium.
Comparator	**Human**: A comparison population exposed to lower levels (or no exposure/exposure below detection levels) of nitrate/nitrite, or to nitrate/nitrite for shorter periods of time.
	Animal: Exposed to vehicle-only treatment.
	In vitro: The populations described above, exposed to an appropriate control.
Outcomes	All health outcomes (both cancer and noncancer). For methemoglobinemia, only studies that inform the quantitative relationship between nitrate/nitrite exposure and methemoglobinemia will be included. In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures. As discussed above, EPA anticipates that a systematic review for health effect categories other than the six identified above (hematological, thyroid, type 1 diabetes, development, reproduction, and cancer) will not be undertaken unless a significant amount of new evidence is identified upon review of references identified during the comprehensive literature search.
***Note:** An iterative approach is used to prioritize evidence from non-mammalian model systems (e.g., fish, amphibians, birds, *C. elegans,* etc.), in vitro, in silico and other types of mechanistic studies based on likelihood to impact evidence synthesis conclusions for human health. Evidence from these studies will be preliminarily tagged during title/abstract screening as “Other Informative Studies” or “Supporting Information” and tagged according to hazard categories and/or types of mechanistic outcomes/pathways. These studies are prioritized for full-text retrieval and evidence synthesis to focus on those studies most important to summarize, based on factors such as robustness of the evidence in humans and animals, directness or relevance of the model systems, and concentrations tested. For example, if robust epidemiological or non-human mammalian evidence is available, then the need to conduct a thorough assessment of individual non-mammalian and mechanistic studies may be diminished unless there are controversial issues to resolve, e.g., related to applicability of animal evidence to humans or shape of dose-response at low exposure levels.	

3.3. KEY SCIENCE ISSUES

The preliminary literature survey identified the following key scientific issues, including potential mode-of-action hypotheses that warrant evaluation in the assessment.

- Nitrate and nitrite are generated endogenously as part of the nitrate-nitrite-nitric oxide cycle that controls the availability of nitric oxide, which is a signaling molecule participating in the regulation of both physiological and pathological processes. The roles of endogenous versus exogenous nitrate and nitrite in toxicity, particularly methemoglobinemia in infants, have been controversial.

- A host of factors can result in increased susceptibility to methemoglobinemia for a large segment of the population: infants under six months old; individuals with higher-than-normal gastric pH; individuals with glucose-6-phosphate dehydrogenase or NADH-dependent methemoglobin reductase deficiency; individuals with diseases such as anemia, cardiovascular disease, lung disease, and sepsis; individuals with abnormal hemoglobin species including carboxyhemoglobin, sulfhemoglobin, and sickle hemoglobin.
- A PBPK model for simulating the kinetics of methemoglobinemia formation after oral exposure to nitrate in adults is available (Zeilmaker et al., 2010; Zeilmaker et al., 1996), and needs to be evaluated for its potential to inform inter-human variability in the dose-response assessment.
    - Previously published assessments by Health Canada (2013), ATSDR (2015), IARC (2010), and WHO (2016), as well as newer animal and epidemiological studies published after 2014 raise the following issues related to cancer risk:
    - Risk associated with intake of nitrates and/or nitrites from cured meats, vegetables, and drinking water may differ because of co-occurrence with antioxidants (e.g., vitamin C, vitamin E) in vegetables, amines in fish and meats, and calcium in drinking water. Consequently, risks associated with dietary intake, intake by drinking water, and total intake may need to be assessed separately.
    - Special populations, such as postmenopausal women, appear to display increased risk associated with intake of nitrate/nitrite.
    - There is significant population variability in ability to reduce salivary nitrate by oral bacteria (e.g., Actinomyces and Veilonella). For example, patients with migraines were shown to have higher abundance of nitrate, nitrite, and nitric oxide reductase genes in their oral bacterial metagenome. In contrast, the use of antiseptic mouthwashes appears to deplete nitrate-reducing oral bacteria and affect some nitrite-mediated biological processes. Individuals from some subgroups may be able to convert more nitrate to nitrite and consequently produce more carcinogenic N-nitroso derivatives.

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